Observational Versus Randomized:

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Letter in response to **Cadrin-Tourigny et al.**, Decreased Mortality With Beta-Blockers in Patients With Heart Failure and Coexisting Atrial Fibrillation: An AF-CHF Substudy; **JACC Heart Fail 2017;10.1016/j.jchf.2016.10.015**

Title: Observational versus randomized - Sliding towards non-evidence based medicine

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Conflicts: DK is the Chief Investigator for the RAte control Therapy Evaluation in permanent Atrial Fibrillation trial (RATE-AF; NCT02391337), the lead for the Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF; NCT00832442), and has received research grants from Menarini, professional development support from Daiichi-Sankyo and lecture fees from AtriCure. MDF reports personal fees from AstraZeneca and grants from Novartis, all outside the submitted work. DGA and GR have nothing to disclose.

We welcome the addition of further data in the field of atrial fibrillation (AF) and heart failure (HF), a combination of conditions that results in difficult management decisions and worse outcomes, both for patients with reduced (1) and preserved left ventricular ejection fraction LVEF.(2) However, it remains important to adhere to some fundamental aspects of evidence-based medicine. Recent years have seen an abundance of subgroup analyses attempting to answer questions relating to treatment effects in non-randomized studies. These analyses, often using propensity matching or other statistical adjustment, have become commonplace and are often mistakenly considered to be as important as randomized controlled trials (RCTs). Regardless of analysis method, observational data should only be used to generate hypotheses about treatment effects (3,4), and we should resist the temptation to analyze datasets simply because of availability. Ignoring the weaknesses of such studies, and incorrect interpretation, can subsequently lead to confounded conclusions.

In the case of the article by Cadrin-Tourigny et al.(5), the patients were not randomized to beta-blockers and hence there is cofounding at both the patient and physician level that hampers external validity. Doctors typically give beta-blockers to patients at lower risk, confirmed in this study as being younger in age, with more non-ischemic cardiomyopathy, less time in AF, and higher use of anticoagulation and defibrillators, all factors associated with lower mortality. Whilst propensity-matched analysis can be useful to mitigate minor differences in demographics, it was not designed to account for different patient populations, or for exposures that interact with the outcome. This has been demonstrated for digoxin therapy (the inverse of beta-blockers, in which clinicians tend to prescribe to higher risk patients), where propensity-matching was unable to replicate the results of RCTs.(6) Confounding may also explain why the authors of this paper found such discrepant findings for death and hospitalization. Further, only 57% of their population were actually in AF at

the time of analysis. We have already shown how effective beta-blockers are in preventing AF (and therefore subsequent adverse outcomes) for HF patients in sinus rhythm.(7) A few methodological issues also arise on detailed review, including the divergence in matched groups, omission of paroxysmal versus persistent AF from the standardized difference plot (with clearly more than 10% difference), and misrepresentation in the abstract about the sample size (n=655 not 1376, with just 95 deaths without beta-blockers and 136 deaths on beta-blockers).

We considered the requirement for AF on the baseline ECG a strength of our previous analysis, which demonstrated a significant interaction in beta-blocker efficacy according to heart rhythm using data from double-blind placebo-controlled RCTs in patients with HF and reduced LVEF.(7) Using systematic, carefully checked and harmonized individual patient data from ten trials, we identified no significant benefit from beta-blockers in over 3000 patients with concomitant AF, consistent across all outcomes studied and based on a published design paper and pre-specified analysis plan.

Where, as a body of clinical scientists, do we go from here? The answer lies in new RCTs, rather than more analyses of observational data.

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